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MARTINELL, J

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 48

Serial Number: 08/078,768
Filing Date: June 16, 1993
Appellant(s): Tullis

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GROUP 1800

Kenneth A. Weber
For Appellant

EXAMINER'S ANSWER

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

This appeal involves claims 64-72.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows.

(a) In the preamble in the Issues section appellant asserts that the claims read on natural and stabilized nucleic acid. This assertion is inaccurate because the claims are all method claims. It is more correct to indicate that the claims mention the use of stabilized nucleic acids and nucleic acids that contain naturally occurring phosphodiester bonds between the monomers.

(b) Item 1 in the Issues section of the brief is inaccurate in stating that no reasons are in the record in connection with the expert declarations (from Drs. Schwartz and Ruth).

(c) Item 2 in the Issues section is incorrect in stating that the examiner has no objective reason for believing that one of skill in the art might need to perform a literature search to identify stabilized oligonucleotides.

(d) The meaning of the term "colorable" in item 3 of the Issues section of the brief is not understood. Additionally, two new references are cited herein to help support the long-standing PTO position in this record that uptake and stability of oligonucleotides into cells are more than imaginary obstacles to success in the specific reduction of synthesis of proteins in cells in vivo or in vitro by intracellular hybridization of oligonucleotides to the coding region of mRNA.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 64-72 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

(a) Tullis et al, "Antisense applications of synthetic nucleic acids," Biotechnology International pp. 79-88 (1992).

(10) New Art

Two new references have been applied in a new ground of rejection under 35 U.S.C. § 112 in this examiner's answer and they are listed below.

(b) Gura, "Antisense has growing pains'" Science 270: 575-577 (1995).

(c) Rojanasakul, "Antisense oligonucleotide therapeutics: drug delivery and targeting," Advanced Drug Delivery Reviews 18: 115-131 (1996).

(11) Grounds of Rejection

The following ground of rejection is applicable to the appealed claims. See the new ground of rejection below.

(12) New Ground of Rejection

This examiner's answer contains the following NEW GROUND OF REJECTION.

Claims 64-72 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the preparation of stabilized forms of oligodeoxyribonucleotides that are phosphotriesters. See M.P.E.P. §§ 706.03(n) and

706.03(z). This is a new ground of rejection made necessary because references (b) and (c) above are newly cited to support the rejection under 35 U.S.C. § 112, first paragraph that was made in the Final Office action. The instant application does not give one of skill in the art guidance in connection with other forms of oligodeoxyribonucleotides that would be stable in vivo (see Office action mailed April 1, 1992, page 2). In the absence of such a teaching, it would require undue experimentation for one of skill in the art to discover and synthesize such compounds. Gura (reference (b) summarizes the problems encountered by those in the "antisense" field over the past several years. Rojanasakul (reference (c)) discusses the problems associated with antisense therapy in more detail than Gura. Among the problems discussed in Rojanasakul are stability, specificity, and cellular uptake (e.g., see the abstract and 118-120). Antisense technology involves the use of usually short nucleotides (usually single stranded DNAs or single stranded DNAs with modified backbones) to inhibit the expression of genes in cells in vivo or in vitro by the mechanism of nucleic acid molecular hybridization inside the cell or by triple helix formation. The instant application concerns an antisense method of specific inhibition of protein synthesis by the nucleic acid molecular hybridization of an oligonucleotide to the coding region of an mRNA inside of a cell, the cell being in an organism, or in an in vitro environment outside of an organism. Gura indicates that a number of problems exist in actually getting these types of methods to work. The Office action mailed April 1, 1992 mentioned that one of these difficulties is the stability of the oligonucleotides in vivo and further indicated that method claims that embraced in vivo use of olig nucleotides were

broader than the enabling disclosure. A later Office action (mailed February 22, 1994) pointed out that references cited by appellant do not address questions of the ability of oligonucleotides to enter cells, the ability of oligonucleotides to specifically hybridize to the target, or in vivo stability. Thus, there are two issues to be decided here. First, does the instant application teach one of skill in the art the full scope of the claimed invention in the sense that the application adequately identifies stabilized oligonucleotides other that those that are phosphotriesters (appellant has been granted a patent (U.S. Patent No. 5,023,243) limited to methods of using the phosphotriesters)? And second, can unmodified deoxyribonucleotides be used in vivo in the claimed methods?

Each of Gura and Rojanasakul support the position that the claims are not enabled for the full scope claimed, for the reasons advanced by the examiner throughout the prosecution history of the application. Additionally, the Gura and Rojanasakul references support earlier assertions of applicant himself wherein appellant indicated that non-modified oligodeoxyribonucleotides would not work in vivo (see references to these statements of appellant hereinbelow).

What follows is a summarization of the long history of the rejection and appellant's responses and then a discussion of the brief.

SUMMARIZATION OF PROSECUTION HISTORY

Appellant's arguments (paper no. 15, pages 3-4) and Exhibits A-E submitted with the response filed October 1, 1992, and pages 6-21 of the brief are not convincing. First, Exhibits A, B, and C were published subsequent to the effective filing date of the instant application. Appellant's argument that these articles ought to be convincing because they show the level of skill in the art at the time the invention was made is not convincing because of the rapid rate of developments in the field of chemical synthesis of oligodeoxyribonucleotides in the early 1980s. Because of the rapid rate of development at that time, the level of skill in the art could change rapidly over a period of only a few months. Thus, the citation of articles published in 1982, 1983, and 1984 in order to establish a level of skill in the art of oligodeoxyribonucleotide synthesis in 1981 is not convincing. Second, appellant's arguments and Exhibits A-E are not sufficient to overcome this rejection because none of Exhibits A-E discusses what is crucial to the use of oligodeoxyribonucleotides in this invention. For example, none of the references discusses (a) the ability of the particular oligodeoxyribonucleotides of any of the references to get into cells, (b) the ability of the particular oligodeoxyribonucleotides of any of the references to hybridize effectively and specifically to a nucleic acid of interest (i.e. a target nucleic acid), or (c) the in vivo stability of any particular oligodeoxyribonucleotides of any of the references. Therefore, given the lack of guidance as to which types of oligodeoxyribonucleotides to use in the instant invention or even the mere mention of

potential candidate oligodeoxyribonucleotides to use and the failure of applicant to establish that one of skill in the art would readily know which oligodeoxyribonucleotide to use in the absence of such a disclosure in the instant application, one of skill in the art would be compelled to undertake undue experimentation in order to practice the invention as claimed. Additionally, the instant application provides no data and provides no methods for actually getting short DNAs or RNAs into cells. Appellant's arguments (paper no. 28), the declarations by Drs. Ruth and Schwartz (filed September 6, 1994), and pages 6-21 of the brief are not convincing because these arguments and declarations do not address the issue of stability of the oligodeoxyribonucleotides in vivo (the declarations are silent on this issue). Paper no. 28 at page 5, first full paragraph asserts that the use of a stabilized nucleic acid is not the inventive principle of the instant invention and that any nucleic acid will work in the claimed method. This argument is most unconvincing in view of the argument made by applicant in the parent application (see patented file of U.S. Patent No. 5,023,243, paper no. 8 (filed February 9, 1984), page 3) wherein applicant says of a reference, "Zamecnik and Stephenson used an unprotected oligonucleotide, which would break down in vivo before having the desired effect." Thus, appellant's assertion that any nucleic acid will work is in conflict with applicant's earlier statement.

Applicant's arguments (paper no. 33) and the declarations by Drs. Schwartz and Ruth (filed April 17, 1995) and the attachments are not convincing. The following is added in rebuttal to arguments advanced by applicant.

(a) Applicant's arguments under section A of paper no. 33 are not convincing. Applicant asserts that, "The Examiner has previously urged that at the time of filing of the parent application in October of 1981, there were no other stabilized oligonucleotides reported in the literature." This assertion is made without reference to where in the file such an "urging" appears. Reference to the Office action mailed December 16, 1992 reveals the actual issue, which is that the instant application fails to guide those of skill in the art as to which oligodeoxyribonucleotides to use. Hence, all of applicant's arguments in connection with the existence of any particular form of oligodeoxyribonucleotide at any time prior to the filing of the instant application are most unconvincing in the absence of a mention or teaching in the application as to how to use them. In fact, the instant application fails to even mention the different forms of oligodeoxyribonucleotides in any specific manner.

(b) Applicant's arguments and remarks in section B of paper no. 33 are most unconvincing because applicant has misidentified the statutory basis of the rejection. Applicant acknowledges (page 8) that the examiner has previously explained to applicant that the statutory basis of the rejection is 35 U.S.C. § 112, first paragraph and does not include 35 U.S.C. § 101 (utility). Accordingly, appellant's arguments in connection with utility are superfluous at best, but are given n weight at all in connection with the rejection under

35 U.S.C. § 112, first paragraph. Appellant additionally argues (page 11) that several references support the notion that intact oligonucleotides can be delivered to animals and isolated cells. This argument is not convincing because each of the articles cited was published subsequent to the effective filing date of the instant application. In addition, the following are noted.

(1) Michelson et al (Exhibit 3) does not disclose the use of a single stranded oligonucleotide, but is concerned only with the stability of a double stranded RNA in vivo. Applicant fails to argue and the declarations fail to reveal how an already double stranded molecule could have any function at all as an antisense molecule, nor do the argument or declarations say what relevance the stability of a double stranded molecule has to the stability of a single stranded molecule. Indeed, applicant simply submits the article, discloses the fact that the article was submitted, and makes no connection between the instant application, claims, or rejection and the article.

(2) Wolff et al (Exhibit 4) is not convincing. First, applicant incorrectly attributes disclosures in Wolff et al to Michelson et al (paper no. 33, page 11 and pages 6 of each of the declarations by Drs. Ruth and Schwartz). Second, the

reference says nothing at all about single stranded oligonucleotides.

(3) Lin et al (Exhibit 5) and the arguments in connection with it are not convincing because the reference does not deal with single stranded oligonucleotides.

(4) Wolff et al (Exhibit 6) and the arguments in connection with it are not convincing because the reference does not deal with single stranded oligonucleotides.

(5) Each of Phillips et al (Exhibit 7), Akabayashi et al (Exhibit 8), and Hijya et al (Exhibit 9) teaches the use of oligodeoxyribonucleotides in vivo. Applicant's reliance on these references to complete the application is insufficient because each of these references was published in 1994, which is after the effective filing date of the instant application.

(c) Applicant argues (paper no. 33, section C) that the examiner misinterpreted a statement made by the inventor during the prosecution history of a prior application. Applicant's argument is unconvincing in the face of the simple, direct, and unambiguous language used by the inventor. Applicant's arguments are further unconvincing in view of published statements under th name f the inventor and others. For example, in the publication by

Tullis et al (Biotechnology International, 1992, reference A15, already of record) state on page 79 that one of the key events in the development of antisense technology was the development was more efficient systems for the synthesis of normal and phosphorous modified oligodeoxyribonucleotides and then goes on to cite a number of references, all of which were published subsequent to the effective filing date of the instant application. (The Beaucage and Caruthers reference is listed as being published in 1980 at page 79, but is listed as published in 1984 in the bibliography. The 1984 date is almost certainly correct because the Beaucage and Caruthers reference is a European Patent application that was filed in 1982.) Additionally, at page 80 (top part of the right hand column), Tullis et al mention problems with uptake and stability of unmodified oligonucleotides and give no clue to the reader to do any of the things that applicant now asserts would have been obvious to anyone of skill in the art in 1981. Thus, the evidence in the record indicates that applicant himself did not know that unmodified oligonucleotides could be used as antisense agents even as late as 1992.

(d) Applicant's argument in paper no. 33, section D is unconvincing. Applicant again incorrectly refers to a hybrid rejection under 35 U.S.C. §§ 101 and 112. Applicant then asserts that, "Once the inventive aspects of the oligonucleotides are recited, the practice of the invention is trivial . . . ." The

argument fails to persuade because the premise is grounded in an incorrect assumption. The very issue here is whether the inventive aspect has been recited. In all the argumentation advanced by applicant, applicant fails to indicate where the application teaches or mentions the use of any specific modified oligonucleotides other than phosphotriesters or the use of unmodified oligonucleotides as antisense agents.

(e) Applicant's arguments (paper no. 33, section E) are unconvincing for reasons given in (a) - (d) above and reasons already of record.

Applicant filed a request for reconsideration on July 20, 1995 in connection with claim 71 only, which claim is directed to a method of inhibiting expression by using nuclease resistant oligonucleotides as antisense agents. Applicant continues to argue that those of skill in the art would know which oligonucleotides to use as antisense agents given the instant disclosure. However, it cannot be agreed that the scant statements in the application (e.g., at page 4) in regard to the use of stabilized forms of oligonucleotides are in any way adequate direction for those of skill in the art as is required under the statute. Indeed, applicant's strenuous argumentation to the effect that those of skill in the art would be expected to do literature searches and would be led from the work of one researcher to another and would see that work on a background of hypothetical information that is only speculated at (e.g., see points 3, 4, and 5 on page 5 of the response filed July 20, 1995) all support the notion that the specification does not teach those of skill in the art how to make and use the invention. This is the standard of the

statute and this is what is expected of the application. It is not enough to hint at what may be desirable, expecting those of skill in the art to perform the undue experimentation that is required to make the invention work. Finally, it is noted that point 6 on page 5 of the response filed July 20, 1995 is not an objective reason, but is an opinion; in fact, it is an opinion unsupported by objective evidence in the record.

DISCUSSION OF THE BRIEF

Appellant's arguments start at page 4. First, the meaning of the term "colorable" in the paragraph bridging pages 4-5 is not understood. Pages 4-6 of the brief foreshadow the sections and arguments that appear later in the brief. The summarization will not be discussed further here.

In section IV: 1 appellant asserts that one of skill would know that only a small class of well known nucleic acid analogs was being referred to in the specification. However, appellant does not point to anything in the application that points one of skill to any particular stabilized analogs of nucleic acids. Appellant frequently attempts to paraphrase the examiner's position on this point, but does not meet the basis for the rejection directly. As stated in the first Office action on the merits, there is no guidance in the application to tell one of sill in the art which forms of oligodeoxyribonucleotides, other than phosphotriesters, would be stable in vivo. Appellant has given no evidence that it would not require undue experimentation to discover such compounds. In fact, the Gura and Rojanasakul references are evidence that undue experimentation would indeed have

been necessary because this problem persists nearly 15 years after the effective filing date of the instant claims.

Appellant asserts that the examiner "cannot maintain this rejection because he was personally unaware that alternative analogs were known in the art." See brief, page 8, second full paragraph. This assertion of appellant is given no weight because the ignorance of the examiner was never used as a reason for the rejection.

Appellant's assert that any stabilized nucleic acid works (e.g., brief, paragraph bridging pages 8-9) is not convincing because it conflicts with each of Gura and Rojanasakul and because appellants have provided no evidence that any stabilized nucleic acid will work in the claimed methods. This argument is made in connection with appellant's assertion that claim 71 does not stand or fall with claims 64-70 and 72.

Section 1 B of the brief (pages 9-13) is not convincing for reasons given above in connection with the declarations of Drs. Schwartz and Ruth and in connection with the discussions of each of the references submitted as evidence in conjunction with those declarations.

Section 2 of the brief cannot be convincing. Appellant asserts that the "specification adequately teaches those of skill in the art which oligonucleotides to use and how to use them to downregulate proteins (sic)." This lengthy argument cannot be convincing in the absence of even a mention of which oligonucleotides to use. The application is more a statement of a goal rather than a teaching of how to reach the goal.

Appellant asserts (section 3, pages 16-17 of the brief) that all stabilized oligonucleotides are taken up by cells. Each of Gura and Rojanasakul are at odds with this sweeping generalization. Hence, appellant's assertion is not convincing.

Section 4 of the brief (pages 18-20) contains another assertion by appellant that all stabilized nucleic acids will bind. Again, each of Gura and Rojanasakul disclose a different view (e.g., Gura at page 575, bottom half of column 1 and Rojanasakul at pages 119-120 (section 4.1)). It is noted that the claims require the specific inhibition of protein synthesis. Since each of Gura and Rojanasakul indicate that hybridization characteristics of stabilized forms of nucleic acids differ from those of non-modified forms and that non-specific effects are seen in cells treated with oligonucleotides, appellant's assertions and arguments cannot be persuasive.

Appellant asserts that the rejection is "obviously a hybrid §§101/112 rejection" (brief, page 21, first full paragraph). This section of the brief (pages 20-23) is given no weight because, as has been emphasized throughout prosecution, there is no rejection in the application of any claim for lack of utility under 35 U.S.C. § 101.

Section 5 B of the brief (pages 23-26) discusses the six references submitted in connection with the declarations of Drs. Schwartz and Ruth. The brief (paragraph bridging pages 23-24 incorrectly states that exhibits 3-9 are six references, the references are numbered as exhibits 3-9 and so there are seven references. These references are discussed in detail above. Several of the references (Michelson et al (Exhibit 3), Wolff et al (Exhibit 4), Lin et al (Exhibit 5), and Wolff et al (Exhibit 6)) do not deal with the use of

single stranded oligonucleotides, so they cannot be used as evidence of the stability of single stranded oligonucleotides. Single stranded oligonucleotides are the only oligonucleotides that can be used in the claimed methods because double stranded oligonucleotides are not free to hybridize with mRNA. The remaining two references (Phillips et al (Exhibit 7), Akabayashi et al (Exhibit 8), and Hijya et al (Exhibit 9)) were each published in 1994, well after the effective filing date of the instant application. Appellant cannot rely on references filed after the effective filing date of the instant claims to complete the enablement requirement (*In re Glass*, 181 USPQ 31, CCPA 1974).

In section 5 C (pages 26-30 of the brief) appellant argues that statements made in the record of the parent application and again in print (Tullis et al, Biotechnology International (1992)) by appellant that unmodified oligonucleotides would not work in vivo because they would break down (see above) are not evidence of what was plainly stated in English. Appellant asserts that these statements are merely "poorly phrased" (see brief, page 26, the bold faced type). Again, on page 27 of the brief, appellant argues a utility rejection that is not in the application. This argument is not relevant because there is no rejection under 35 U.S.C. § 101 extant or extinct in the instant application. Additionally, appellant urges (last full paragraph on page 27 of the brief) that one of skill in the art need only just add more unmodified nucleic acid to make the method work. This argument is most unconvincing in view of appellant's own statements (in this entire record, the only statements by the inventor in connection with use of unmodified nucleic acids are the two alluded to above), the statements in each of Gura and R janasakul, and the absence of any

teaching of "just adding more" in the instant application. The application is to be a guide to those of skill in the art of how to practice the invention. Appellant has pointed to no guidance in the application as filed for "just adding more." Finally, appellant (brief, page 28, second full paragraph) claims that the sentence is poorly worded and can be interpreted differently. The sentence is, "Zamecnik and Stephenson used an unprotected oligonucleotide, which would break down in vivo before having the desired effect." To this the only reply can be, A is A. Appellant urges that appellant should be able to retract misstatements. Fair enough. However, the inventor did not say this once, but at least twice and one of those times it was published work (and it was more than a decade after the effective filing date of the instant claims). We have not heard from the inventor about this since and there is no evidence in the record that the inventor's own statements were incorrect. Much less do we have an indication in the application as filed that the inventor contemplated the "just add more" method. For these reasons, the simple, direct, plain, unambiguous, and clear wording of the statements are taken at face value.

Section 6 of the brief (pages 30-31) concerns itself with utility under 35 U.S.C. § 101 and will not be addressed in the absence of such a rejection in the record.

Section 7 of the brief (pages 31-34) is not convincing because it misstates the issue. Appellant asserts (paragraph bridging pages 31-32) that the type of nucleic acid used to bind the mRNA is irrelevant. This is incorrect. A casual review of this long record will reveal that that is precisely what is relevant. The relevance of this as an issue is embodied in the exposition f same in the rejecti n first made on April 1, 1992.

(13) Period of Response to New Ground of Rejection

In view of the new ground of rejection, appellant is given a period of TWO MONTHS from the mailing date of this examiner's answer within which to file a reply to any new ground of rejection. Such reply may include any amendment or material appropriate to the new ground of rejection. Prosecution otherwise remains closed. Failure to respond to the new ground of rejection will result in dismissal of the appeal of the claims so rejected.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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